REMARKS

Claims 1, 3-6, and 8-45 are pending in the application and are under active consideration.

Claim 1 has been amended to recite a method of eliciting a humoral immune response against a hepatitis C virus (HCV) E2 or E1E2 antigen comprising the step of (a) administering to a subject (i) a composition comprising an isolated polynucleotide encoding an HCV E1E2 antigen, wherein the E1E2 antigen consists of an HCV E1 polypeptide and an HCV E2 polypeptide and optionally an HCV p7 polypeptide, and further wherein the E1E2 antigen encoded by the polynucleotide consists of a sequence selected from the group consisting of a sequence of amino acids corresponding to amino acids 192-715 and optionally amino acids 747-809 numbered relative to the HCV-1 polyprotein, a sequence of amino acids corresponding to amino acids 192-661 and optionally amino acids 747-809 numbered relative to the HCV-1 polyprotein, and a sequence of amino acids corresponding to amino acids 192-674 and optionally amino acids 747-809 numbered relative to the HCV-1 polyprotein, or (ii) a composition comprising an isolated polynucleotide encoding a truncated E2 antigen, wherein said truncated E2 antigen does not include the p7 polypeptide, wherein the E2 antigen encoded by the polynucleotide consists of a sequence selected from the group consisting of a sequence of amino acids corresponding to amino acids 384-715 numbered relative to the HCV-1 polyprotein, a sequence of amino acids corresponding to amino acids 384-661 numbered relative to the HCV-1 polyprotein, and a sequence of amino acids corresponding to amino acids 384-674 numbered relative to the HCV-1 polyprotein, wherein the E2 or E1E2 antigen encoded by the polynucleotide is produced intracellularly and not secreted when expressed in cells of the subject. Support for the amendment can be found in the specification, for example, at page 3, lines 5-8; and at page 17, line 21 through page 18, line 9. Accordingly, the specification provides adequate support for this amendment. Entry of the amendment is respectfully requested.

Amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of

record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Rejection under 35 U.S.C. § 103

A. Houghton and Fields Virology

Claims 1, 4-6, 8-10, 14, 15, 17, and 26 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the references of Houghton et al. (EP0318216; hereinafter "Houghton") and Fields Virology. Houghton is cited for teaching delivery of polynucleotides encoding envelope proteins. Fields is cited for showing that E1 and E2 and the properties associated with them were known in the art at the time of the invention. In maintaining the rejection, the Final Office Action alleges:

> Applicant has not argued that the sizes of HCV E1 and E2 are not those as listed in Fields (page 1037 Figure 1). It was known that E1 and E2 are not secreted and that deletion mutants are secreted (Fields page 1037 column 2, top and bottom). This is an inherent property of the proteins, not a new ground of rejection. Houghton suggest polynucleotides from envelope proteins (E1 and E2), not secreted forms. (Final Office Action, page 3).

Applicants respectfully traverse the rejection under 35 U.S.C. § 103 on the following grounds.

Claim 1, as amended, is drawn to a method of eliciting a humoral immune response against a hepatitis C virus (HCV) E2 or E1E2 antigen comprising administering to a subject a composition comprising an isolated polynucleotide encoding a truncated HCV E2 antigen or an HCV E1E2 antigen consisting of an HCV E1 polypeptide, a truncated HCV E2 polypeptide, and optionally an HCV p7 polypeptide, wherein the E2 or E1E2 antigen encoded by the polynucleotide is produced intracellularly and not secreted when expressed in cells of the subject. Some of the dependent claims further require that the humoral immune response generate neutralization of binding (NOB) antibodies.

The instant application provides evidence that higher levels of NOB antibodies can be produced in a subject by administering polynucleotides encoding E2 antigens and E1E2 antigens that are expressed intracellularly compared to polynucleotides encoding

antigens that are secreted. See specification, for example, at Examples 1-4. Furthermore, higher titers of NOB antibodies are shown for intracellularly produced truncated E2 antigens than full-length E2 antigens (see specification, *e.g.*, at Table 2). None of the cited references teach methods of eliciting a humoral immune response in a subject by administering polynucleotides encoding truncated E2 polypeptides or E1E2 antigens comprising such truncated E2 polypeptides that are produced intracellularly. Moreover, prior art teaches away from the intracellular production of truncated E2 polypeptides as acknowledged by the Examiner (see Final Office Action, page 3).

Houghton fails to describe or suggest any method using polynucleotides encoding truncated E2 antigens or E1E2 antigens containing truncated E2 polypeptides, as claimed. Nor does Houghton describe eliciting a humoral immune response with a polynucleotide encoding truncated E2 that is produced intracellularly and not secreted when expressed in cells of a subject. Moreover, Houghton is silent on the importance of delivering polynucleotides that encode truncated E2 antigens or E1E2 antigens comprising truncated E2 polypeptides that are specifically produced intracellularly and not secreted, wherein a humoral immune response generates NOB antibodies in the subject.

Fields Virology also fails to teach or suggest any method of administration of polynucleotides encoding truncated E2 or E1E2 antigens comprising a truncated E2 polypeptide for eliciting a humoral immune response against hepatitis C virus. Fields Virology also does not describe intracellular production of truncated polypeptides, or the importance of producing truncated E2 polypeptides intracellularly for production of NOB antibodies. Therefore, no combination of the cited references teaches the methods of claims 1, 4-6, 8-10, 14, 15, 17, and 26.

For at least these reasons, withdrawal of the rejection of claims 1, 4-6, 8-10, 14, 15, 17, and 26 under 35 U.S.C. § 103 is respectfully requested.

B. Houghton and Fields Virology, further in view of Ishii

In addition, claims 3 and 18-25 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Houghton et al. (*supra*), and Fields

Virology, and further in view of Ishii et al. (Hepatology (1998) 28:1117-1120; hereinafter "Ishii"). Ishii has been cited for teaching that antibodies to envelope (E2) give rise to NOB antibodies. Applicants respectfully traverse the rejection under 35 U.S.C. § 103 on the following grounds.

Claims 3 and 18-25 are directed to methods of eliciting a humoral immune response that generates NOB antibodies.

As mentioned above, the combination of Houghton and Fields Virology fails to teach methods of eliciting a humoral immune response comprising administering polynucleotides encoding truncated E2 antigens or E1E1 antigens comprising truncated E2 polypeptides that are produced intracellularly, as claimed. The secondary reference of Ishii also fails to teach such methods. Rather, Ishii discovered that the presence of NOB antibodies in HCV infected patients correlated with the eventual recovery of patients from HCV infection. Ishii, however, merely identified a problem in the art without identifying any solution. Ishii fails to disclose or suggest any method of eliciting NOB antibodies in patients not producing such antibodies naturally. The instant application solves this problem in the art by disclosing methods for raising NOB antibody titers in HCV infected individuals. Therefore, no combination of the cited references teaches the claimed methods.

For at least these reasons, withdrawal of the rejection of claims 3 and 18-25 under 35 U.S.C. § 103 is respectfully requested.

C. Houghton and Fields Virology, further in view of Fomsgaard (Nielsen) or Singh

In addition, claims 1, 3-6, 8-17, and 27-45 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Houghton et al. (*supra*), and Fields Virology, and further in view of Fomsgaard et al. (APMIS (1998) 106:636-646 (Applicants assume this is the reference intended); hereinafter "Fomsgaard") or Singh et al. (Vaccine (1998) 16:1822-1827; hereinafter "Singh"). In particular, the Final Office Action alleges that claims 28-40 include the same limitations as claims 11-13, 16, and 27

and that these claims are rejected for the same reasons stated above. Applicants respectfully traverse the rejection under 35 U.S.C. § 103 on the following grounds.

The secondary references of Fomsgaard and Singh fail to fill the gaps in the references of Houghton et al. (*supra*), and Fields Virology. Neither Fomsgaard nor Singh pertain to HCV infection. Fomsgaard describes methods of DNA vaccination against HIV and HBV. Singh pertains to the use of PLG microparticles and MF59 adjuvant in vaccinations against herpes simplex virus. Notably absent from either reference is any discussion of methods for eliciting a humoral immune response against any HCV antigens, let alone any method for producing NOB antibodies. Therefore, no combination of the cited references teaches the claimed methods.

For at least these reasons, withdrawal of the rejection of claims 1, 3-6, 8-17, and 27-45 under 35 U.S.C. § 103 is respectfully requested.

D. No Motivation to Combine the Teachings of the Cited References

In the absence of some teaching or suggestion in the cited references concerning methods of eliciting a humoral immune response against hepatitis C virus (HCV) E2 or E1E2 antigens as claimed, the Examiner has presented no more than an improper hindsight reconstruction of the present invention.

It is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. *See, e.g., In re Kotzab,* 55 USPQ2d 1313, 1317 (Fed. Cir. 2000, emphasis added):

> While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection **cannot** be predicated on the mere identification [in the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no

knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

Virtually all inventions are combinations of elements that can be individually identified in multiple references. See, e.g., *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) noting that the Office cannot rely on a high level of skill in the art to overcome the differences between the selected elements in the references, it cannot rely on a high level of skill in the art to provide the necessary motivation; *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), affirming that common knowledge and common sense are not the specialized knowledge and expertise necessary to establish a motivation to arrive at the claimed invention.

Thus, the requirement is not whether each claimed element can be identified individually in a reference but, rather, whether the Examiner can show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 47 USPQ2d at 1458. In the pending case, the Office has not met this burden.

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Since the suggestion or motivation to combine the references to arrive at the claimed invention is not in the references, the Examiner is required to cite to some knowledge generally available to one of ordinary skill in the art for the motivation to combine the references. (MPEP 2143). It is respectfully submitted that the Examiner has not provided such knowledge. Instead, the Examiner has merely asserted that because (1) Houghton and Fields Virology teach E1 and E2 antigens and (2) Ishii teaches that the presence of NOB antibodies in HCV infected patients correlates with resolution of HCV infection, it would have been obvious to combine the references to arrive at the claimed invention.

Without a suggestion to modify the references evident in the prior art, as well as a lack of a reasonable expectation of success, the only conclusion supported by the record

is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). As also stated by the Court of Appeals for the Federal Circuit "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Therefore, the Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103.

For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

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